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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/693,555	10/20/00	KORNMAN	K MSA-009.01(2

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FOLEY HOAG & ELIOT LLP
ONE POST OFFICE SQUARE
BOSTON MA 02109-2170

EXAMINER	
KYLES, C	
ART UNIT	**PAPER NUMBER**
1655	5

DATE MAILED: 09/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/693,555	Applicant(s) KORNMAN ET AL.	
	Examiner Carla Myers	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-84* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Application No.: 09/693555

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s)

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

1. ***RESTRICTION***

Prior to setting forth the restriction requirement, it is pointed out that Applicants have presented the methods of claims 17-32 and 42-57, claims 33-41, claims 58-64 and claims 65-74 in improper Markush format. See Ex parte Markush, 1925 C.D. 126 and In re Weber, 198 USPQ 334. The method claims are improperly joined as the claimed methods require the detection of distinct target molecules (i.e. IL-1 nucleic acids, IL-1 proteins, TNF nucleic acids and TNF proteins). A reference against one target molecule would not be a reference against the other target molecule . Therefore, the restriction will be set forth for each of the various groups, irrespective of the improper format of the claims, because the claims do not recite proper species. **Upon election, Applicants are required to amend the claims to set forth only the elected inventive groups.**

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-8 and 80-84, drawn to methods to detect a predisposition to adverse pregnancy outcome, classified in Class 435, subclass 6.

II. Claims 9-16 and 75-59, drawn to kits comprising primers, classified in Class 536, subclass 24.33.

III. Claims 17-32 and 42-57, drawn to methods of treatment and methods for selecting a therapeutic regimen by detecting an IL-1 genotype, classified in Class 514, subclasses 1 and 44.

IV. Claims 17-32 and 42-57, drawn to methods for selecting a therapeutic regimen by detecting an TNF-alpha genotype, classified in Class 514, subclasses 1 and 44.

V. Claims 33-41, drawn to method for determining the effectiveness of treatment by measuring IL-1 protein levels, classified in Class 435, subclass 7.1.

VI. Claims 33-41, drawn to method for determining the effectiveness of treatment by measuring IL-1 nucleic acid levels, classified in Class 435, subclass 6.

VII. Claims 33-41, drawn to method for determining the effectiveness of treatment by measuring IL-1 protein activity, classified in Class 435, subclass 4.

VIII. Claims 33-41, drawn to method for determining the effectiveness of treatment by measuring TNF-alpha protein levels, classified in Class 435, subclass 7.1.

IX. Claims 33-41, drawn to method for determining the effectiveness of treatment by measuring TNF-alpha nucleic acid levels, classified in Class 435, subclass 6.

X. Claims 33-41, drawn to method for determining the effectiveness of treatment by measuring TNF-alpha protein activity, classified in Class 435, subclass 4.

XI. Claims 58-64, drawn to a method for detecting a compound that effects the interaction of IL-1 and an IL-1 binding partner, classified in Class 435, subclass 7.1.

XII. Claims 58-64, drawn to a method for detecting a compound that effects the interaction of TNF-alpha and an TNF-alpha binding partner, classified in Class 435, subclass 7.1.

XIII. Claims 65-74, drawn to methods for identifying compounds that decrease IL-1 activity, classified in Class 435, subclass 4.

XIV. Claims 65-74, drawn to methods for identifying compounds that decrease IL-1 activity, classified in Class 435, subclass 4.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the kits of claim II can be used in a materially different process such as for methods which analyze the sequence of the IL-1 gene and methods which diagnose other types of diseases.

Inventions I and III-XIV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to patentably distinct methods which require different reagents, and/or have different objectives. Invention I is drawn to methods for diagnosing a predisposition to an adverse pregnancy outcome or LBW and requires detecting an IL-1A (-511) or IL-1A (+4845) allele. Invention III is drawn to a method for selecting an appropriate therapeutic for an individual by selecting a therapeutic that compensates for a causative functional mutation in an IL-1 gene that is in linkage disequilibrium with the LBW associated allele and thereby invention III requires identifying a causative functional IL-1 mutation and selecting a therapeutic that

compensates for said mutation. Invention IV is drawn to a method for selecting an appropriate therapeutic for an individual by selecting a therapeutic that compensates for a causative functional mutation in an TNF-alpha gene that is in linkage disequilibrium with the LBW associated allele and thereby invention III requires identifying a causative functional TNF-alpha mutation and selecting a therapeutic that compensates for said mutation Inventions V-X are drawn to methods for determining the effectiveness of treating a LBW subject and requires administering a drug to a subject and detecting IL-1 protein levels (invention V), IL-1 nucleic acid levels (invention VI), IL-1 activity (invention VII), TNF-alpha protein levels (invention VIII), TNF-alpha nucleic acid levels (invention IX), or TNF-alpha activity (invention X). Drugs which alter IL-1 protein levels, IL-1 nucleic acid levels, IL-1 activity, TNF-alpha protein levels, TNF-alpha nucleic acid levels and TNF-alpha activity have different mechanisms of action and are patentably distinct from one another, and methods for detecting protein levels, nucleic acid levels and IL-1 and TNF-alpha activity involve different reagents and require performing different method steps. Invention XI is drawn to a method for screening for a therapeutic for treating a LBW disorder and requires the use of IL-1 protein, an IL-1 binding partner and a test compound and requires determining whether a test compound prevents or allows for the formation of a complex between IL-1 and an IL-1 binding partner. Invention XII is drawn to a method for screening for a therapeutic for treating a LBW disorder and requires the use of TNF-alpha protein, an TNF-alpha binding partner and a test compound and requires determining whether a test compound prevents or allows for the formation of a complex between TNF-alpha and an

TNF-alpha binding partner. Invention XIII is drawn to a method for identifying a therapeutic for treating a LBW disorder and requires the use of a cell or cell extract which expresses IL-1 and the use of a test compound and involves determining whether the test compound decreases agonist or antagonist bioactivity. Invention XIV is drawn to a method for identifying a therapeutic for treating a LBW disorder and requires the use of a cell or cell extract which expresses TNF-alpha and the use of a test compound and involves determining whether the test compound decreases agonist or antagonist bioactivity.

Inventions II and III-XIV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not disclosed as capable of use together because the kits of invention II are not required to practice the methods of inventions III-XIV and the kits of invention II can be used in materially different processes such as in general methods for determining the sequence of the IL-1 gene and in methods for diagnosing other types of diseases.

2. ***Sequence Election Requirement Applicable to Groups 1-4***

In addition, each invention detailed above reads on patentably distinct inventions drawn to multiple SEQ ID Numbers. The sequences are patentably distinct because they are unrelated sequences, and a further restriction is applied to each invention. For an elected invention drawn to a nucleic acid or amino acid sequences, Applicants must further elect a single nucleic acid or amino acid sequence. For example, if Applicant elects invention I,

Applicant must further elect a single nucleic acid sequence selected from the group of SEQ ID Nos: 1-18.

It is noted that nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.14.

3. Because these inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-XIV require different searches that are not co-extensive, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

4. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-25 for the reasons set forth on the attached Notice to Comply with Requirements For Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures. Applicants must comply with the requirements of 37 CFR 1.821-1.825 in response to this Office action. In particular, Applicant is required to submit a CRF and paper copy of the Sequence Listing containing the disclosed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOS into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

September 19, 2001

CARLA J. MYERS
PRIMARY EXAMINER